LITERATURE-RELATED DISCOVERY: POTENTIAL TREATMENTS AND PREVENTATIVES FOR SARS

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ABSTRACT
Literature-related discovery (LRD) is the linking of two or more literature concepts (that have not been linked previously in the literature; i.e., disjoint) in order to produce novel, interesting, plausible, and intelligible connections (i.e., potential discovery). The open discovery systems (ODS) component of LRD starts with an unsolved problem, and generates solutions to that problem through potential discovery. ODS LRD has been used to identify potential treatments or preventative actions for challenging medical problems, among myriad other applications.

Severe acute respiratory syndrome (SARS) was the first pandemic of the 21st century. The appearance of SARS seems to have involved: 1) a zoonotic origin for SARS-coronavirus (SARS-CoV) (e.g., horseshoe bats and/or Chiroptera as one wildlife reservoir); 2) transmission to intermediate hosts (e.g., civet cats, raccoon dogs); 3) human contact with these intermediate hosts in Southern China (Guangdong Province, Fall 2002) and subsequent cross-species transmission of SARS-CoV to humans; 4) transmission of the virus through both non-hospital personal contact and hospital staff contact; and, 5) global transmission of the virus via travelers from affected regions in Asia to other countries. SARS was eventually controlled through increased hygienic measures (e.g., face mask protection, frequent hand washing, living quarter disinfection), travel restrictions, and quarantine. According to recent reviews of SARS, ***none of the drugs that were used during the pandemic worked***.

For the present paper, SARS was selected as the first application of LRD to an ***infectious*** disease. The first goal of this research was to identify non-drug non-surgical treatments that would 1) prevent the occurrence, or 2) reduce the progression rate, or 3) stop/reverse the progression of SARS. The MeSH taxonomy of Medline was used to restrict potential discoveries to selected semantic classes, and to identify potential discoveries efficiently. The second goal was to generate large amounts of potential discovery in more than an order of magnitude less time than required for the author's previous Raynaud's Phenomenon LRD study. To enhance the volume of potential discovery, databases were used in addition to Medline. These included the Science Citation Index (SCI) and a full text database for the first time. Because of the richness of the full text, 'surgical' queries were developed that targeted the exact types of potential discovery of interest while eliminating clutter more efficiently.

1. INTRODUCTION

1.1 Overview and Background

To summarize the core methodology, LRD is the linking of two or more literature concepts (that have not been linked previously in the literature; i.e., disjoint) in order to produce novel, interesting, plausible, and intelligible connections (i.e., potential discovery). The open discovery systems (ODS) component of LRD starts with an unsolved problem, and generates solutions to that problem through potential discovery. ODS LRD has been used to identify potential treatments or preventative actions for challenging medical problems, among myriad other applications. The closed discovery systems (CDS) component of LRD starts with an unsolved problem and a potential solution, and generates potential mechanisms that link the solution to the problem. Typically, ODS has proven to be more challenging than CDS because of its open-ended nature, but each has its own unique challenges. ODS is the only approach that will be used for the present study.

Two points should be emphasized before proceeding further. First, linking of disjoint literatures is a necessary but not sufficient condition for discovery. There needs to be value-added in the novel concept(s) that results. Second, while 'potential discovery' is used in this paper and throughout the LRD literature, 'hypothesis' is more accurate. What results from these LRD 'discovery' studies are hypotheses that have to be tested in the laboratory/field before they can be properly termed 'discoveries'.

A 2009 review paper by the author showed that, while a number of LRD published papers claimed to have generated potential discovery, essentially none of these claims could be validated [1]. The only published LRD potential discovery claims that could be validated as credible hypotheses were in a journal Special Issue devoted to LRD (e.g., [[2], [3]) The four medical papers in this Special Issue describe the application of ODS LRD to four ***chronic*** diseases: Raynaud's Phenomenon (RP), cataracts, Parkinson's Disease (PD), and Multiple Sclerosis (MS).

The present paper presents a comprehensive approach to systematic acceleration of potential discovery and innovation, and demonstrates the generation of large amounts of potential discovery for prevention/treatment of an ***infectious*** disease: SARS. The general issues of potential discovery and innovation in the LRD context are discussed in the first paper of the Special Issue [4], and the general

methodology for this discovery approach was shown in the second paper of the Special Issue [5]. The SARS biomedical background has been published in a detailed review article, and the interested reader is referred to that article [6].

The present paper provides an overview of the etiology and challenges of SARS, then presents a retrieval and analysis of the core SARS literature and literatures related directly to the core SARS literature (e.g., immune system component literatures). These related literatures might contain the seeds of potential discovery (treatments and preventive measures) for SARS, and some examples of potential discovery are presented. For the first time, full text analysis was included for the related literatures. This provided a substantial increase in the volume of potential discovery retrieved. Also, examples of interesting but non-discovery (i.e., potential innovation) concepts from the core SARS literature are presented, since they have practical value in their own right.

The four previous medical papers in the LRD Special Issue also included potential discovery from indirectly-related literatures. The indirectly-related literatures for this infectious disease proof-of-principle demonstration were not examined for the following reason. The amount of potential discovery retrieved from the directly related literature alone (including the full text directly related literature) is voluminous. A major challenge is to select those combinations of potential discoveries that provide the maximum synergy. Until these potential discoveries have been exploited properly, there is little practical need of going to indirectly related literatures to search for more potential discovery. In the practical situation, even the potential innovation as defined above has not been exploited properly, and accelerating these potential innovations should be the first order of business.

1.2 Purpose of Study

SARS is a contagious disease that resulted in the hospitalization of about 8000 people world-wide in 2002-2003, and resulted in the deaths of about 800 people. According to recent reviews of the pandemic, ***none of the drugs worked***. Those who recovered did so by natural means; their immune systems were sufficiently strong to eliminate the viral attack. Many were aided by public health interventions (e.g., face mask protection, frequent hand washing, living quarter disinfection, travel restrictions, and quarantine) as well.

The subject of SARS was selected for study because of its pandemic nature, and its apparent intractability to all drug treatments. The main goal of this study was to identify non-drug non-surgical treatments that would 1) prevent or delay the onset,

or 2) reduce the progression rate, or 3) stop/reverse the progression, of SARS. For much of the study, Medline was used as the data source, and the MeSH taxonomy of Medline was used to restrict potential discoveries to selected semantic classes.

The second goal was to generate large amounts of potential discovery in more than an order of magnitude less time than required for the RP study. To enhance the volume of potential discovery, a full text database was used for the first time. Because of the richness of the full text, 'surgical' queries were developed that targeted the exact types of potential discovery of interest while eliminating clutter more efficiently. The 'surgical' nature of these queries compensated for the additional 'noise' characteristic of the more voluminous full text. However, since the full text database (Science Direct) did not have an associated MeSH taxonomy, the MeSH taxonomy headings were essentially used as text phrases to restrict SARS treatment and prevention potential discoveries to selected substances. The SCI was also used to search for discovery, and again the MeSH taxonomy headings were used as text phrases to restrict potential discoveries to selected substances. Approximately four times as many records were retrieved from Medline when MeSH terms were included in the query compared to using only terms in the title or Abstract, due to the greater choice of potential discovery substances. This means the SCI or SD queries as presently constituted will retrieve only about 25% of the records that are possible using MeSH to define the substance pool.

The discovery generation methodology has been developed to the point where ODS LRD problems can be solved with no results or knowledge of any prior work. Before the specific approach and results are described, the medical issues for SARS that served as targets for the discovery search query will be summarized.

1.3 SARS Medical Issues

The first pandemic of the 21st century was the outbreak of SARS caused by the SARS-CoV. As far as is known, this outbreak was not due to the deliberate release of the SARS-CoV, but rather was a naturally occurring event. The appearance of SARS seems to have involved: 1) a zoonotic origin for SARS-CoV (e.g., horseshoe bats and/or Chiroptera as one wildlife reservoir [7]); 2) transmission to intermediate hosts (e.g., civet cats, raccoon dogs [8]); 3) human contact with these intermediate hosts in Southern China [Guangdong Province, Fall 2002] and subsequent cross-species transmission of the coronavirus to humans [8]; 4) transmission of the virus through both non-hospital personal contact and hospital staff contact [9]; and, 5) global transmission of the virus via travelers from affected

regions in Asia to other countries. SARS was eventually controlled through increased hygienic measures (e.g., face mask protection, frequent hand washing, living quarter disinfection), travel restrictions, and quarantine.

A number of recent reviews have focused on different components of the above SARS etiology, with the central focus of 1) identifying common characteristics of those who succumbed to the disease in order to 2) develop treatment targets for future outbreaks. A careful reading of these reviews shows that the humoral and cellular components of the adaptive immune system of those who succumbed were deficient on presentation and deteriorated thereafter. There is controversy about whether adequate antiviral interferons were generated during the innate response, but there is common agreement that the switch from innate to adaptive immunity was defective [10; 11; 12; 13; 14; 15; 16; 17; 18; 19; 20, 21; 22; 23]

Specifically, those who succumbed from SARS-CoV infection tended to have the following characteristics:

- **Older age**
- **Male gender**
- **Presence of comorbidities**
- **Elevated LDH or C-reactive protein/ high initial lactate dehydrogenase level**
- **Higher initial viral load of SARS coronavirus**
- **Elevated neutrophil count/neutrophilia**
- **High levels of chemokines CXCl10 and IL-18**
- **High levels of IL-6, IL-8, and MCP-1**
- **Significant increase in the TH2 cytokines IL-4, IL-5, IL-10**
- **Increased levels of IP-10, MIG and IL-8**
- **Lower levels/deficient anti-SARS spike antibody production**
- **Lymphopenia/low counts of CD4 and CD8 at presentation**
- **Reduced ACE2 expression**
- **Reduced levels of IL-12p70 and TNF-alpha (relative to positive outcome)**
- **Positive RT-PCR on nasopharyngeal aspirate samples**
- **Elevated pulse rate**
- **Raised serum albumin**
- **Raised serum creatinine phosphokinase (CPK) levels**
- **Increased serum creatine kinase, and urea**
- **Deviated ISG and immunoglobulin gene expression levels**

These characteristics served as the targets to be improved by potential discoveries.

2. APPROACH

Figure 2 in the second paper of the Special Issue (Methodology) [5] is a flow chart that outlines the steps used in the present study. In summary, the core SARS literature is retrieved, the retrieved literature is clustered to identify the main generic themes, literatures are retrieved for the main generic themes, the SARS core literature is subtracted, the retrieved literatures for the main generic themes are intersected with the literature of desired solution types (e.g., non-drug substances), then searches for discovery are performed in the net retrieved literature for the given classes of substances. The specific steps employed are as follows.

2.1 Core SARS Literature

The core SARS literature was retrieved from two databases (SCI and Medline), using the following as a query (Steps 1 and 2 in Figure 2 of the Methodology paper [5]).

(Severe-Acute-Respiratory-Syndrome OR SARS-Virus OR (SARS AND (coronavirus OR infect* OR virus* OR viral OR epidemic* OR epidemiology OR antibodies OR antibody OR vaccine* OR influenza OR pandemic* OR outbreak* OR syndrome)) OR SARS-patient* OR SARS-transmission OR SARS-CoV)

2.2. Directly Related Literature

Multiple grouping approaches were used to identify the main generic themes of the core SARS literature: document clustering, auto-correlation mapping of phrases, and factor matrix analysis of phrases, using the Vantage Point software package [24]. These grouping techniques were applied to retrievals from both databases, and no significant differences were observed.

The main problem was deciding which hierarchical level of grouping to use for the query. Initially, groupings at the lowest level of detail (e.g., CD4, CD8, IL1, IL2, IFN-gamma, etc) were examined. However, a detailed examination of the SARS literature showed inconsistencies in the desired directions of some of these items, based on clinical observations and data. This led to examination of groupings at a higher level of aggregation (e.g., inhibit viral replication, enhance humoral immunity, improve cell-mediated immunity, increase Th1, etc), which could accommodate different directions at the lowest level of detail while achieving the targets represented by the higher level of aggregation.

To retrieve the directly related literature, from which potential discovery would be extracted, this higher level query was applied to the search engines of three databases: SCI, Medline, and SD. The first two of these databases provide Abstracts as the major text source, and SD provides full text. Since the SD analysis took place a few months after the SCI and Medline analyses, the initial query was modified slightly to exploit the SD search engine features. Appendix 1 contains the full SCI and Medline queries, and Appendix 2 contains the full SD query. The unique features of each are explained in the appendices.

There were two types of fundamental terms in the full query, and examples from the more abbreviated SD query will be presented here.

TYPE 1
(((inhibit PRE/5 "virus entry") OR (inhibit* PRE/5 "viral entry") OR (inhibit* W/15 replicat* W/15 virus) OR (inhibit* W/15 replicat* W/15 viral)) AND (potent PRE/15 "antiviral activity"))*

TYPE 2
(((enhanc PRE/5 "humoral immun*") AND (enhanc* PRE/5 "humoral response*") AND ((enhanc* PRE/5 "antibod* response*") OR (enhanc* PRE/5 "antibod* production") OR (enhanc* PRE/5 "virus neutraliz*") OR (enhanc* PRE/5 "viral neutraliz*"))) OR ((enhanc* PRE/5 "cellular immun*") AND (enhanc* PRE/5 "cell mediated immun*") AND ((enhanc* PRE/5 CD4) OR (enhanc* PRE/5 CD8) OR (enhanc* PRE/5 "t cell response*") OR (enhanc* PRE/5 "t cell immune response*"))) OR ((enhanc* PRE/5 "innate immun*") AND (enhanc* PRE/5 "innate antiviral") AND ((enhanc* PRE/5 "antiviral activity") OR (enhanc* PRE/5 "antiviral response*"))))*

Type 1 focused on inhibiting viral entry to healthy cells and/or inhibiting their replication, whereas Type 2 focused on improving immune system component performance. As contrasted to the Type 2 query, the specific terms used in the Type 1 query were limited to those shown above. 'A PRE/5 B' is a precedence relation, and means that term A precedes term B, with a spacing ranging from zero (adjacency) to five words. 'A W/15 B' is a proximity relation, and means that term A is within 15 words of term B. This form of the query provided highly ***'relevant'*** retrievals.

Discussion of Relevance

What does 'relevant' mean in the present context? The purpose of this study is to identify potential discovery and innovation. For this purpose, 'relevant' is interpreted as any article that contains a potential discovery or innovation candidate. What is potential discovery? It is the linking of two or more literature concepts (that have not been linked previously in the literature; i.e., disjoint) in order to produce novel, interesting, plausible, and intelligible connections. A potential discovery ***candidate*** is an ***interesting*** linkage that has to be vetted against prior knowledge to validate ***disjointness***. In practice, a major roadblock is defining 'prior' knowledge, and in particular the databases that will be used to represent 'prior' knowledge for the vetting process and how these databases will be interpreted. To make the problem tractable, only the main source databases are selected for the prior knowledge determination. In the present case, the same three major sources that were used in previous LRD medical studies have been selected for the prior knowledge determination: SCI; Medline; patent database as represented by Derwent Innovation Index (DII).

In previous LRD studies, the SCI and Medline drove the discovery algorithms. Because of the large amount of overlap between SCI and Medline in the biological and medical literatures, a substance/behavior that resulted from the discovery algorithm as a potential discovery candidate had a reasonable chance of being termed a potential discovery when only SCI and Medline were used to validate prior art. The major rejections due to prior art came from the patent database (DII), and that has proven to be true in the present study. In the previous LRD studies, prior art was assumed to occur if the potential discovery candidate and the disease under examination co-occurred in the same article or through the referencing process. In most cases, co-occurrence of these terms in Medline and the SCI tended to reflect actual conceptual linkages ***based on evidence***. In a not insignificant number of patents, **claims were made for linkages based on no evidence presented in the patent**. Therefore, in the present study, co-occurrence of terms in the patent literature did not automatically rule out potential discovery. Each co-occurrence in the patent literature (and in Medline and SCI as well) was examined to see 1) whether the co-occurrence reflected a conceptual linkage; 2) whether the conceptual linkage was supported by any evidence, or 3) whether the conceptual linkage was merely an assertion with no factual underpinnings.

When the Type 1 query shown above was applied to full text, reasonable numbers of relevant articles were retrieved. When the Type 1 query was applied to Abstracts, the articles retrieved were highly relevant, but the numbers retrieved (as will be shown) were miniscule. To obtain more articles when searching the

Abstracts, a modified Type 1 query was generated. This modified form changed the 'AND' (in the query above) to an 'OR', a much less restrictive condition. This resulted in an order of magnitude more retrieved and relevant articles (when searching Abstracts), although still small compared to the retrievals obtained from searching full text.

Type 2 queries focused on enhancing the performance of the different components of the immune system. There were a number of variants of the Type 2 query shown above that were examined, where 'enhanced' was replaced by 'induced', 'stimulated', 'increased', 'improved', 'activated', 'regulated', 'modulated', etc.

3. RESULTS

3.1 Numbers of Retrievals from Different Source Databases

3.1.1. SCI

Appendix 1 shows the form of the query used to generate the SCI results. The Type 2 entry under the T component is for 'Improv*', but the full query added blocks that replaced 'Improv*' with Enhanc* or Induc* or Stimulat* or Increas* or Activat* or Regulat*. Obviously, other such terms could be identified and used as well, but these terms were deemed adequate for the present proof-of-principle demonstration.

Format of Query

Before discussing the other query terms in Appendix 1, further discussion on the format of terms in the Improv* block is required. The SCI search engine does not have adjacency/proximity search capability presently. The only search capabilities are co-occurrence in a selected field or among all fields (e.g., A SAME B, or A AND B). To overcome this deficiency, the author developed an algorithm that would provide such capability [25]. In the algorithm, SCI stopwords are used to set spacing between terms. Thus, a query term of the form [improv*-of-humoral-immun*] will retrieve those records containing variants of improv* that precede variants of 'humoral-immun*' with one word intercalated. The intercalated word could be any word, not just the stopword used in the query. As can be seen from the terms in Appendix 1, the actual query used did not go beyond precedence spacings of two words, but a larger production-oriented study could use greater spacings between the terms of interest. This would retrieve far more records, and lead to more candidate potential discoveries.

In Appendix 1, the S block of terms represents the core SARS records, and its inclusion as a negation expression insures the records retrieved are disjoint from the core SARS literature. The blocks listed under C are the types of substances/behaviors considered for discovery. They consist of records from non-drug journals as shown, and records that contain non-drug substances. The value of including the journals is that their records could include substances/behaviors not identified in the substances/behaviors blocks (i.e., pre-specified lists of substances/behaviors). Obviously, many more substances/behaviors could be added to the list in a more comprehensive production-oriented study.

Application of the full query to the SCI/SSCI database (1989-2008, Articles and Reviews) yielded 662 records. The records were sampled for 'relevancy' to discovery or innovation, using the definitions of relevancy as discussed previously. Approximately 85% were judged to be 'relevant' (potential discovery candidates). In addition, the 7000 most recent papers in the SCI that cited the 662 records were retrieved. These citing papers covered approximately the seven year period 2002-2008, and about 50% were judged to be relevant. In the previous LRD studies on medical topics, before the ability to retrieve all the papers that cite an initial retrieval became available in the SCI, only spot checks could be done of papers that cited potential discovery candidates. Not only are papers that cite potential discovery candidates good potential discovery candidates themselves, but the author's preliminary (unpublished) experiments show many different types of citation linkages (e.g., papers that share references) to potential discovery candidates will identify good potential discovery candidates.

3.1.2. Medline

Application of the query to the Medline database yielded 1149 records. While the version of the Medline database used (through the Web of Knowledge search engine) goes back to 1950, it effectively started in about 1975, when Abstracts were introduced. The records retrieved were sampled for 'relevancy' to discovery or innovation, using the definitions of relevancy as discussed previously. Approximately 80% were judged to be 'relevant' (potential discovery or innovation candidates). There is much overlap between Medline and the SCI.

3.1.3. Science Direct

Application of the appropriate query from Appendix 1 to the Science Direct database (1999-2008) yielded different types of results, depending on which field was searched, and some of these findings are reported in Table 1. The retrieval results among SCI, Medline, and Science Direct are not comparable due to the different journal coverage of each database. Specific examples of potential discovery from each of these databases will be shown later in the present Results section.

TABLE 1. SCIENCE DIRECT – LITERATURE-RELATED DISCOVERY

QUERY	UNMOD. QUERY	MOD. QUERY	UNMOD. QUERY	FT/ABS	MOD

	ABS REC	% REL	ABS REC	% REL	FLTX REC	% REL	NORM	NORM
INHIBIT* ACETABULARIA	1	100	31	90	170	90	172.3	5.56
INHIBIT* EUGLENIDA	5	100	60	90	243	90	49.26	4.1
INHIBIT* PLANKTON	7	100	28	90	350	90	50.68	12.67
ENHANC* ACETABULARIA	0		14	60	90	80	INF	6.52
ENHANC* EUGLENIDA	0		29	70	129	80	INF	4.51
ENHANC* PLANKTON	0		18	40	170	80	INF	9.57
INDUC* ACETABULARIA	0		56	30	464	50	INF	8.4
INDUC* EUGLENIDA	0		101	40	749	60	INF	7.52
INDUC* PLANKTON	1	100	79	70	944	40	956.75	12.11
STIMULAT* ACETABULARIA	0		37	50	142	60	INF	3.89
STIMULAT* EUGLENDIA	0		49	60	235	50	INF	4.86
STIMULAT* PLANKTON	0		34	80	265	60	INF	7.9

INCREAS* ACETABULARIA	0		35	40	192	40	INF	5.56
INCREAS* EUGLENDIA	0		58	40	303	50	INF	5.29
INCREAS* PLANKTON	0		44	40	291	60	INF	6.7

In Table 1, the Science Direct results are for the three components of the Type 1 query. The first row (INHIBIT*ACETABULARIA) reflects the intersection of the terms for the 'inhibit' group and the 'Acetabularia' group listed in the Appendix 2 query. The second and third rows substitute the Euglendia and Plankton groups for the Acetabularia group.

For the first row, the second column (UNMOD QUERY – ABSREC) contains the number of records retrieved when the full text query was applied to the Abstract field. The full text query was designed to provide 'surgical' targeting of key phrase relations in the ***full text***, contains the ***intersections*** of a number of proximal relations, and is a rather ***restrictive*** condition. Applied to the full text, the query is very effective, but it is ***far too restrictive for the Abstract field***, as the results show. Very few records are retrieved, and they are all relevant (Column 3). Essentially no records were retrieved in this column for any of the Type 2 queries, since the Type 2 queries are even more restrictive (more intersecting terms) than the Type 1 query.

Column 4 (MOD. QUERY - ABSREC) contains records retrieved using the modified Type 1 query applied to the Abstract field. All occurrences of 'AND' were replaced with 'OR'. On average, about an order of magnitude more records were retrieved with the modified query compared to the full text query, ***but the numbers are still small***. The relevance of the retrieved records is still quite high. For the Type 2 query components (not shown), the Column 4 retrievals were about half as much for the 'enhance' group, about twice as much for the 'induce' group, about the same for the 'stimulate' group, and about the same for the 'increase' group. There were overlaps among the groups, and search engine limitations did not allow estimation of the degree of overlap.

Column 5 is the relevance percentage of the Column 4 retrievals. It is highest for the 'inhibit' group, is about 60% for the 'enhance' group, and is about 50% for the other three (Type 2) groups.

Column 6 (UNMOD. QUERY - FLTXREC) represents the retrievals for the full text query of Appendix 2 applied to the full text. They are almost an order of magnitude larger than those of Column 4, and the relevance percentage (Column 7) is almost the same as that for the Abstracts in Column 5. The percentage is highest for the 'inhibit' group, is about 80% for the 'enhance' group, and is about 50% for the other three (Type 2) groups.

Column 8 (FT/ABS-NORM) is the ratio of full text retrievals to Abstract retrievals (normalized to the total numbers of full text and Abstract records in the database) using the restricted form of the full text query for each, and Column 9 is the same ratio where the less restricted form of the query was used to search the Abstracts.

The bottom line is that many potential discovery candidates have been retrieved. Many more are possible: increasing the substance base (through more non-drug items or by inclusion of drugs) would probably increase the number of candidates by an order of magnitude; increasing the number of terms in the query would enhance the retrieval; relaxing the proximity conditions would increase the retrieval; relaxing the intersection requirements would increase the retrieval; adding further types of citation linkages would increase the retrieval. A major factor in the high relevance fractions achieved is the form of the query terms; they were not used in any previous LRD studies, but will become a fixture in future studies.

There is another possible route to retrieving more potential discovery candidates, but the magnitude is difficult to estimate. The approach described above for the query focused mainly on substance/behavior impacts on the immune system mentioned in the article. These could be direct or indirect impacts, but the co-occurrence of the substance/behavior and the immune system impact was required.

The growing field of psychoneuroimmunoendocrinology assumes these major systems/networks are inter-related. One could impact the immune system directly, or could impact the immune system indirectly through the CNS and endocrine systems, and perhaps through psychological intervention. Indirect impacts of a substance SUB on the immune system IMM of the form SUB--->CNS; CNS--->IMM, where the semi-colon denotes separation into two papers, would not be retrieved, since the substance and the immune system are not mentioned in the

same paper. This could be an important route for immune system impacts, and needs to be tested in a future study. The author is presently doing another type of study in psychoneuroimmunoendocrinology, and the results should provide some insight into how better to approach the indirect impacts on the immune system.

3.2. Examples of Retrievals from Different Literatures

This remainder of this section contains representative examples of potential discovery from literatures related directly to the core SARS literature. Before proceeding to analyses, a few illustrative examples from the core SARS literature restricted to semantic classes will be presented. While these are not discovery, they nevertheless reflect the types of impact that the non-drug approaches could potentially have for delaying or preventing the onset of SARS. In addition, as will be discussed later, some of these core concepts are prime candidates for innovation.

For example, “Aurintricarboxylic acid (ATA) has been shown to inhibit the replication of viruses from several different families, including ….. the coronavirus causing severe acute respiratory syndrome. Vaccinia virus replication is significantly abrogated upon ATA treatment, which is associated with the inhibition of early viral gene transcription. This inhibitory effect may be attributed to two findings. First, ATA blocks the phosphorylation of extracellular signal-regulated kinase 1/2, an event shown to be essential for vaccinia virus replication. Second, ATA inhibits the phosphatase activity of the viral enzyme H1L, which is required to initiate viral transcription. Thus, ATA inhibits vaccinia virus replication by targeting both cellular and viral factors essential for the early stage of replication” [26].

As another example, “we identified that three widely used Chinese medicinal herbs of the family Polygonaceae inhibited the interaction of SARS-CoV S protein and ACE2. The IC50 values for Radix et Rhizoma Rhei (the root tubers of Rheum officinale Baill.), Radix Polygoni multiflori (the root tubers of Polygonum multiflorum Thunb.), and Caulis Polygom multiflori (the vines of P. multiflorum Thunb.) ranged from I to 10 [Lg/ml]. Emodin, an anthraquinone compound derived from genus Rheum and Polygonum, significantly blocked the S protein and ACE2 interaction in a dose-dependent manner. It also inhibited the infectivity of S protein-pseudotyped retrovirus to Vero E6 cells. These findings suggested that emodin may be considered as a potential lead therapeutic agent in the treatment of SARS" [27].

3.2.1. Non-Drug Concepts in the Core SARS Literature

a.”Cimicifuga rhizoma, Meliae cortex, Coptidis rhizoma, Phellodendron cortex and Sophora subprostrata radix decreased the MHV production and the intracellular viral RNA and protein expression with EC50 values ranging from 2.0 to 27.5 mu g/ml. These extracts also significantly decreased PEDV production and less dramatically decreased vesicular stomatitis virus (VSV) production in vitro. The extracts selected strongly inhibited MHV replication and could be potential candidates for new anti-coronavirus drugs” [28].

b.”221 phytocompounds were evaluated for activity against anti-severe acute respiratory syndrome associated coronavirus (SARS-CoV) activities using a cell-based assay measuring SARS-CoV-induced cytopathogenic effect on Vero E6 cells. Betulinic acid (13) and savinin (16) were competitive inhibitors of SARS-CoV 3CL protease with K-i values = 8.2 +/- 0.7 and 9.1 +/- 2.4 mu M, respectively. Our findings suggest that specific abietane-type diterpenoids and lignoids exhibit strong anti-SARS-CoV effects.” [29].

c.”….. a natural compound called quercetin-3-beta-galacto side was identified as an inhibitor of the protease [*(3CL(pro))*]….. With the help of molecular modeling, eight new derivatives of the natural product were designed and synthesized……This study not only reveals a new class of compounds as potential drug leads against the SARS virus, but also provides a solid understanding of the mechanism of inhibition against the target enzyme.” [30].

d.”alpha,beta-unsaturated peptidomimetics, anilides, metal-conjugated compounds, boronic acids, quinolinecarboxylate derivatives, thiophenecarboxylates, phthalhydrazide-substituted ketoglutamine analogues, isatin and natural products have been identified as potent inhibitors of the SARS-CoV main protease…… Some of these inhibitors could be developed into potential drug candidates, which may provide a solution to combat possible reoccurrence of the SARS and other life-threatening viruses with 3CL proteases.” [31].

e.”…..we screened a natural product library consisting of 720 compounds for inhibitory activity against 3CLPro. Two compounds in the library were found to be inhibitive: tannic acid (IC50 = 3 mu M) and 3-isotheaflavin-3-gallate (TF2B) (IC50 = 7 mu M). These two compounds belong to a group of natural polyphenols found in tea……Only theaflavin-3,3'-digallate (TF3) was found to be a 3CLPro inhibitor. This study has resulted in the identification of new compounds that are effective 3CLPro inhibitors.” [32].

3.2.2. Non-Drug Potential Discovery Concepts in the SCI Retrieved by Query

a."The purpose of this study was to test fermentation, for its products of a Chinese medicinal mushroom, Ganoderma lucidum, cultured by submerged fermentation for its effect on growth performance and immunocompetence in weanling piglets…..GLF up-regulated the cell-mediated immune response related cytokines (IL-2, IFN-gamma, and TNF-alpha) expression in different lymphoid tissues…..a supplementation with 50 mg GLF per kg feed also inhibited PCV-2 virus amplification, and ameliorated lymphocyte depletion in different lymphoid tissues."[33].

b."Jacalin, an (alpha-O-glycoside of the disaccharide Thomsen-Friedenreich antigen (galactose (beta 1-3 N-acetylgalactosamine, T-antigen)-specific lectin from jackfruit seeds, has been shown to induce mitogenic responses and to block infection by HIV-1 in CD4(+) T lymphocytes…..Based on these findings, we propose a new, immunoregulatory model for Jacalin, wherein glycosylation-dependent interactions of Jacalin with CD45 on T cells elevate TCR-mediated signaling, which thereby up-regulate T cell activation thresholds and Th1/Th2 cytokine secretion." [34].

c."Administration of sulforaphane significantly enhanced the production of IL-2 and IFN-gamma in metastatic tumor-bearing animals. In addition, sulforaphane significantly downregulated the serum levels of proinflammatory cytokines such as IL-1 beta, IL-6, TNF-alpha, and GM-CSF during metastasis. These data clearly suggest that sulforaphane effectively inhibited the spread of metastatic tumor cells through the stimulation of CMI, upregulation of IL-2 and IFN-gamma, and downregulation of proinflammatory cytokines IL-1 beta, IL-6, TNF-alpha, and GM-CSF." [35].

d. "Immunomodulatory activity of methanolic extract of M. koenigii leaves was evaluated on humoral and cell mediated immune response to ovalbumin,……the extract holds promise as immunomodulatory agent, which acts by stimulating humoral immunity and phagocytic function." [36].

e."Tinospora cordifolia (guduchi) is a widely used shrub in ayurvedic systems of medicine known to possess immunomodulatory properties……the aqueous extract of T. cordifolia was found to enhance phagocytosis in vitro. The aqueous and ethanolic extracts also induced an increase in antibody production in vivo." [37].

f.”Fucoidan, a sulfated polysaccharide isolated from an edible brown alga Undaria pinnatifida…..the effects of the fucoidan were examined on in vivo viral replication and the host's immune defense system…..Phagocytic activity of macrophages and B cell blastogenesis in vitro were significantly stimulated by the fucoidan…..oral administration of the fucoidan produced the augmentation of NK activity…..CTL activity…was also enhanced by oral administration of the fucoidan. The production of neutralizing antibodies in the mice…was significantly promoted during the oral administration of the fucoidan for 3 weeks. These results suggested that oral intake of the fucoidan might take the protective effects through direct inhibition of viral replication and stimulation of both innate and adaptive immune defense functions.” [38].

g.”Atractylodes macrocephala Koidz (AMK)…..markedly stimulated lymphocyte proliferation, antibody production, and cytokine secretion in mouse splenocytes. In particular, the samples showed the ability to induce the preferential stimulation of Th1 type, rather than Th2 type T lymphocytes…..Our findings suggest that the glycoprotein(s) might play critical roles in modulating immune-response induction, and could potentially be used as medicinal and pharmacological agents.” [39].

h.” A potent anti-influenza virus activity was discovered in summer leaves of Japanese wasabi [(Wasabia japonica)]. The ethanol extracts inhibited influenza virus replication regardless of the hemagglutinin antigen type. Therefore, such extracts are expected to be a promising source of a novel anti-influenza virus agent.” [40].

i.” In this paper, we describe the purification of an antiviral peptide from seeds of Sorghum bicolor L…..The peptide designated 2 kD peptide strongly inhibited the replication of herpes simplex virus type I (HSV-1)…..Similar results were observed when the 2 kD peptide was assayed against bovine herpes virus (BHV), an enveloped virus like HSV-1….these results indicate that the 2 kD peptide was able not only to inhibit the initiation and the spread of infection, but also had an in vitro prophylactic effect against HSV-1 infection.” [41].

3.2.3. Non-Drug Potential Discovery Concepts in the SCI Retrieved by Citing Papers

a.” We investigated the ***synergistic*** effect of pidotimod and red ginseng acidic polysaccharide (RGAP) from Panax ginseng C.A. Meyer on humoral immune response challenged by lipopolysaccharide (LPS) and sheep red blood cells

(SRBC) in immunosuppressed mice. ***Combined treatment with pidotimod and RGAP significantly increased the number of plaque-forming cells in the spleen*** in response to both LPS and SRBC, while ***treatment with either pidotimod or RGAP individually had no such effect***……These results indicate that combined treatment with pidotimod and RGAP has an immunostimulatory effect in a synergistic manner on antibody response to challenge with LPS and SRBC without toxic changes." [42].

b." …..the inhibition of influenza virus replication was measured. Myrica rubra leaf ethanol extract showed anti-influenza virus activity irrespective of the hemagglutinin antigen type in the influenza virus type A (H1N1), its subtype (H3N2), and type B." [43].

c." oral intake of L. paracasei NCC2461 by aged mice enhanced the specific adaptive immune response to in vivo antigenic challenge without altering other cellular and humoral immune responses. The poor responsiveness to antigenic challenge, frequently observed in elderly people, may be improved by supplementation with L. paracasei NCC2461." [44]

d."…..the anti-viral activity of methanol and aqueous extracts from thirty medicinal plants were examined in this study……Extracts prepared from different plants were tested the antiviral activity against influenza viruses…..methanol extract of Asarum sieboldii inhibited the H5N1 influenza viruses from the infected cells." [45].

e."our lab has successfully isolated a 1,6-di-O-caffeoyl-beta-D-glucopyranoside, monomer named Caffeoyl Glycoside (CC) from the roots of Picrorhiza scrophulariiflora (Kutki)…..CC Stimulated cell proliferation of splenocytes and peritoneal macrophages, and enhanced the cytotoxicity of natural killer (NK) cells significantly. CC also increased CD4 and CD8 cell populations……CC has immunomodulatory activity by regulating expression of Th1 and Th2 related cytokines. Taken together, these results indicated that CC might have potential effects in regulating the immune system, and this compound might be a useful immunotherapeutic agent in treating various immunity-related diseases." [46].

3.2.4. Vaccine Adjuvants – Medline

a." The mucosal adjuvanticity of Korean mistletoe lectin C (KML-C) was investigated in mice intranasally immunized with inactivated influenza virus (H1N1)……KML-C increased influenza-specific antibodies with dominant IgG1

subclass in serum, IgG in genital secretions and IgA in saliva, and significantly enhanced influenza-specific lymphocyte proliferation and cytotoxic activity in spleens and in mediastinal lymph nodes. When KML-C was used as a mucosal adjuvant, mice were completely protected from mortality after the challenge with a homologous (H1N1) mouse-adapted influenza virus. After challenge with heterologous (H3N2) influenza virus the level of heterosubtypic immunity in KML-C-treated mice was comparable to that of mice that received CTB as adjuvant. These findings suggest that KML-C may be used as an effective mucosal adjuvant." [47].

b." Seeds of a Chinese traditional medicine plant, Cochinchina momordica were used in the present study for the improvement of influenza vaccine (H5N1) in chicken. Crude extraction from Cochinchina momordica seed (ECMS) was obtained by ethanol extraction method……Results revealed that all ECMS groups numerically increased the antibody levels while 10 and 20 microg/dose groups significantly ($P<0.05$) enhanced total IgG antibody on day 28, when compared with control…..It is concluded that ECMS has potential to improve the immune responses and deserve further study as an adjuvant. [48]

c."…..Ag85B of mycobacteria, which cross-reacts among mycobacteria species, elicits helper T-cell type 1 (Th1) immune responses as a novel adjuvant. These responses were enhanced in mice sensitized by BCG before vaccination. Since most humans have been sensitized by spontaneous infections or by vaccination with mycobacteria, these findings indicate that Ag85B is a promising adjuvant for enhancing Th1 immune responses of vaccine candidates. [49]

d."…..we evaluated the immunomodulatory effects of probiotic Bacillus cereus var. toyoi on the systemic immunity of piglets……Blood samples of probiotic-treated piglets showed a significantly lower frequency of CD8(high)/CD3+ T cells and CD8(low)/CD3+ T cells and a significant higher CD4+/CD8+ ratio. IL-4 and IFN-gamma production of polyclonally stimulated PBMCs was on average higher in the probiotic group. Specific proliferative responses of PBMCs to Influenza vaccination antigens were significantly higher and antibody titers against H3N2 Influenza and Mycoplasma vaccination antigens were on average higher in the probiotic group. In conclusion, B. cereus var. toyoi therefore alters the immune status of piglets as indicated by changes in the ratios as well as functionalities of systemic immune cell populations." [50].

3.2.5. Non-Drug Potential Discovery Concepts in Science Direct

a." We recently demonstrated that kefir modulates the immune response in mice, increasing the number of IgA+ cells in the intestinal and bronchial mucosa and the phagocytic activity of peritoneal and pulmonary macrophages. The aim of this study was to further characterize the immunomodulating capacity of the two fractions of kefir…..Different components of kefir have an in vivo role as oral biotherapeutic substances capable of stimulating immune cells of the innate immune system, to down-regulate the Th2 immune phenotype or to promote cell-mediated immune responses against tumours and also against intracellular pathogenic infections." [51].

b."Lentinan also possesses antiviral activity due to an induction of interferon-γ production. Lentinan enhances host resistance against infections with bacteria as well as fungi, parasites, and viruses, including the agent of AIDS. Lentinan reduced the toxicity of AZT (a drug commonly used for treating HIV carriers and AIDS patients). Prevention of the onset of AIDS symptoms through potentiation of host defense is now being actively investigated both experimentally and clinically" [52].

c."Here we demonstrate that a polyphenol rich extract (CYSTUS052) from the Mediterranean plant Cistus incanus exerts a potent anti-influenza virus activity in A549 or MDCK cell cultures infected with prototype avian and human influenza strains of different subtypes……On a molecular basis the protective effect of CYSTUS052 appears to be mainly due to binding of the polymeric polyphenol components of the extract to the virus surface, thereby inhibiting binding of the hemagglutinin to cellular receptors. Thus, a local application of CYSTUS052 at the viral entry routes may be a promising approach that may help to protect from influenza virus infections." [53].

Because the purpose of the SARS study was to demonstrate an approach, and not necessarily to be comprehensive, a number of shortcuts were taken. Not all possible semantic categories for potential discoveries were identified, only the most obvious. Relatively few terms were selected for the queries; many more were available. Not all retrieved records were examined; only enough to demonstrate the quality of results. The potential expansion to indirectly related literatures using both text linking and citation linking described previously was not done. Thus, the results obtained should be viewed as the tip of a very large iceberg.

4.1. Discussion and Conclusions

In previous medical applications of LRD, the discovery approach was to cluster the disease literature into groups of disease characteristics, generate combinatorials of intra-group characteristics (essentially synonyms), construct a discovery query from these combinatorials, and apply the query to non-drug substances/behaviors. In the present application, a somewhat different tactical approach was taken. Since the characteristics of those who had succumbed to SARS tended to be sub-optimal performance of different immune system components, the query combined the immune system components at a higher aggregation level with terminology designed to improve this performance (e.g., enhance humoral immunity). Such a query structure allowed a large number of potential discovery candidates to be identified. As the previous paragraph shows, much more is possible in terms of potential discovery volume.

The picture from the handful of potential discoveries reported in this paper (and the hundreds of additional potential discoveries possible with a properly resourced study) is a synergy of lifestyle/ dietary practices that could be interpreted as anti-SARS. **Along with non-discovery items such as** *Aurintricarboxylic acid (ATA), Emodin (an anthraquinone compound derived from genus Rheum and Polygonum), Cimicifuga rhizoma, Meliae cortex, Coptidis rhizoma, Phellodendron cortex, Sophora subprostrata radix, Betulinic acid, savinin, abietane-type diterpenoids and lignoids, quercetin-3-beta-galacto side, d.alpha,beta-unsaturated peptidomimetics, anilides, metal-conjugated compounds, boronic acids, quinolinecarboxylate derivatives, thiophenecarboxylates, phthalhydrazide-substituted ketoglutamine analogues, isatin, tannic acid, and 3-isotheaflavin-3-gallate (TF2B)* **are potential discovery items such as** *Ganoderma lucidum, Jacalin, Sulforaphane, methanolic extract of M. koenigii leaves, Tinospora cordifolia, Fucoidan, Atractylodes macrocephala Koidz, Wasabia japonica, seeds of Sorghum bicolor L, pidotimod and red ginseng acidic polysaccharide (RGAP), Myrica rubra leaf ethanol extract, L. paracasei NCC2461, methanol extract of Asarum sieboldii, Caffeoyl Glycoside, and adjuvants Korean mistletoe lectin C, Cochinchina momordica seed, Ag85B, probiotic Bacillus cereus var. toyoi, Kefir, Lentinan, polyphenol rich extract (CYSTUS052) from the Mediterranean plant Cistus incanus.* As stated above, more laboratory tests and field trials would have to be done on all these items to insure that they are anti-SARS and safe, but these preliminary literature-based results offer some promise of what is possible.

There is a major disconnect between the absence of therapies presently or potentially available on all the major medical Web sites (and in SARS mainstream journal review papers), and the potential therapies suggested by what has already been demonstrated in the core SARS literature, much less what this study has

generated from the related literatures. Few medical Web sites even mention any of the approaches shown in the SARS core results section. The core literature and related literature potential discoveries and innovations have the potential to evolve into mainline medical treatments.

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APPENDIX 1 – SCI AND MEDLINE QUERIES

The query has two components: (T NOT S) and C. T represents the technical query terms of interest, and S represents the technical query terms defining the SARS core literature. T NOT S will retrieve those records of interest in the total database, excluding records found in the SARS core literature. C mainly represents the substances/behaviors that are in the potential discovery pool. C also includes the journals whose articles tend to focus on such substances/behaviors, and thus would expand the substance pool for potential discovery beyond the listing of substances below.

The standard SCI or Medline search engine does not have a proximity or adjacency search feature. The author generated an algorithm that would allow such capability for these databases [Kostoff et al, 2006]. In this algorithm, inclusion of stopwords (e.g., an, of, the, etc) in the query translates as wildcards. Thus, if A, B are query search terms, then the query string A-of-B is interpreted by the computer as any string where A precedes B and A and B are separated by one word (e.g., improve*-of-viral could be 'improve SARS viral' or 'improved antibody viral', etc). As can be seen below, the queries contain up to two sequential stopwords (of-of). Had longer stopword strings been included, more records would have been retrieved.

QUERY = (T NOT S) AND C

T.
(improv*-humoral-immun* OR improv*-antibod*-response* OR improv*-humoral-response* OR improv*-antibod*-level* OR improv*-virus-neutraliz* OR improv*-viral-neutraliz* OR improv*-neutraliz*-antibod* OR improv*-antibod*-production OR improv*-antibod*-bind*) OR (improv*-of-humoral-immun* OR improv*-of-antibod*-response* OR improv*-of-humoral-response* OR improv*-of-antibod*-level* OR improv*-of-virus-neutraliz* OR improv*-of-viral-neutraliz* OR improv*-of-neutraliz*-antibod* OR improv*-of-antibod*-production OR improv*-of-antibod*-bind*) OR (improv*-of-of-humoral-immun* OR improv*-of-of-antibod*-response* OR improv*-of-of-humoral-response* OR improv*-of-of-antibod*-level* OR improv*-of-of-virus-neutraliz* OR improv*-of-of-viral-neutraliz* OR improv*-of-of-neutraliz*-antibod* OR improv*-of-of-antibod*-production OR improv*-of-of-antibod*-bind*)

OR

(improv*-cellular-immun* OR improv*-cell-mediated-immun* OR improv*-CD4 OR improv*-CD8 OR improv*-t-cell-response* OR improv*-t-cell-immune-response* OR improv*-th1) OR (improv*-of-cellular-immun* OR improv*-of-cell-mediated-immun* OR improv*-of-CD4 OR improv*-of-CD8 OR improv*-of-t-cell-response* OR improv*-of-t-cell-immune-response* OR improv*-of-th1) OR (improv*-of-of-cellular-immun* OR improv*-of-of-cell-mediated-immun* OR improv*-of-of-CD4 OR improv*-of-of-CD8 OR improv*-of-of-t-cell-response* OR improv*-of-of-t-cell-immune-response* OR improv*-of-of-th1)

OR

(inhibit*-virus-entry OR inhibit*-viral-entry OR inhibit*-of-virus-entry OR inhibit*-of-viral-entry OR inhibit*-of-of-virus-entry OR inhibit*-of-of-viral-entry OR (inhibit*-replication SAME (virus OR viral)) OR (inhibit*-of-replication SAME (virus OR viral)) OR (inhibit*-of-of-replication SAME (virus OR viral)))

S.
(Severe-Acute-Respiratory-Syndrome OR SARS-Virus OR (SARS AND (coronavirus OR infect* OR virus* OR viral OR epidemic* OR epidemiology OR antibodies OR antibody OR vaccine* OR influenza OR pandemic* OR outbreak* OR syndrome)) OR SARS-patient* OR SARS-transmission OR SARS-CoV)

C.
SO=(Alternative Medicine Review Or Complementary "And" Alternative Approaches To Biomedicine Or Journal Of Alternative "And" Complementary Medicine Or Complementary Therapies In Medicine Or Evidence Based Complementary "And" Alternative Medicine Or Journal Of Complementary Medicine Or Planta Medica Or Ethnopharmacologie Sources Methodes Objectives Or Journal Of Ethnopharmacology Or Biologically Active Phytochemicals In Food Or Dietary Phytochemicals In Cancer Prevention "And" Treatment Or Food Phytochemicals For Cancer Prevention I Or Food Phytochemicals For Cancer Prevention Ii Or Phytochemicals "And" Health Or Phytochemicals Aging "And" Health Or Phytochemical Potential Of Tropical Plants Or Phytochemistry Of Medicinal Plants Or Phytochemistry Of Plants Used In Traditional Medicine Or Phytotherapy Research Or Second World Congress On Medicinal "And" Aromatic Plants For Human Welfare Wocmap 2 Pharmacognosy Pharmacology Phytomedicines Toxicology Or Phytomedicine Or Fitoterapia Or Potential Health Benefits Of Citrus Or Journal Of Medicinal Plants Research)

OR

TS=(Acetabularia OR Achlya OR Acupressure OR Acupuncture OR Algae OR Alkaloid* OR Allium OR Angiosperms OR Anthocerotophyta OR Anthocyanins OR Antiviral-Plant* OR Aphanomyces OR Apigenin OR Arachis-Hypogaea OR Ascophyllum OR Avena-Sativa OR Bed-Rest OR Benzoflavones OR Beta-Naphthoflavone OR Biflavonoids OR Brassica OR Bryophyta OR Caffeine OR Caloric-Restrict* OR Calorie-Restrict*) OR (Capsicum OR Carbohydrate-Restricted OR Cascara OR Castor-Oil OR Catechin* OR Caulerpa OR Cereal* OR Chalcone* OR Chara OR Characeae OR Chia OR Chicory OR Chimera OR Chive* OR Chlamydomonas OR Chlorella OR Chlorophyll* OR Chondrus OR Citrus OR Clove-Oil OR Cod-Liver-Oil OR Coffee OR Complementary-Medicine OR Corn-Oil) OR (Cottonseed-Oil OR Cotyledon OR Coumarin* OR Coumestrol OR Croton-Oil OR Cryptophyta OR Cucumis-Sativus OR Curare OR Cyanophora OR Daucus-Carota OR Diabetic-Diet OR Dietary-Supplement* OR Diosmin OR Chinese-Herbal OR Edible-Plant* OR Electroacupuncture OR Entera-Nutrition OR Equisetum OR Ethnobotany OR Ethnomedicin* OR Ethnopharmacology OR Euglena OR Euglenida) OR (Fabaceae OR Fagopyrum OR Fat-Restricted OR Ferns OR Fish-Oil* OR Flavanone* OR Flavone* OR Flavonoid* OR Flavonolignan* OR Flavonol* OR Flavoxate OR Flax* OR Flowering-Tops OR Fruit* OR Fucus OR Garlic OR Genistein OR Ginseng OR Gracilaria OR Gymnosperm* OR Helianthus OR Hepatophyta OR Herb* OR Hesperidin OR Holistic-Health) OR (Homeopathy OR Hops OR Hordeum OR Iodized-Oil OR Ipecac OR Isoflavone* OR Kaempferol* OR Kelp OR Lagenidium OR Laminaria OR Laurencia OR Leaf OR Leaves OR Lecithin* OR Lettuce OR Lichens OR Lignan* OR Limonoid* OR Linseed-Oil OR Lolium OR Luteolin OR Lycopersicon-Esculentum OR Lycopodiaceae OR Macrocystis OR Medicago-Sativa OR Medicinal-Plant* OR Mediterranean-Diet) OR (Meristem OR Mustard-Plant OR Mycorrhizae OR Naturopathy OR Neolignan* OR Nitella OR Nutrition-Therapy OR Nutritional-Support OR Nuts OR Ochromonas OR Olive* OR Omega-3-Fatty-Acid* OR Onions OR Oomycetes OR Opium OR Oryza-Sativa OR Panicum OR Parenteral-Nutrition OR Peas OR Pectin* OR Peronospora OR Phloem) OR (Phytochemical* OR Phytophthora OR Phytoplankton OR Phytotherapy OR Plankton OR Plant-Component* OR Plant-Epidermis OR Plant-Extract* OR Plant-Famil*Or Plant-Leaves OR Plant-Oils OR Plant-Preparation* OR Plant-Root* OR Plant-Shoot* OR Plant-Stem* OR Plant-Tuber* OR Plocamium OR Podophyllin OR Polyine*) OR (Polyphenol* OR Porphyra OR Porphyridium OR Proanthocyanidin* OR Protein-Restricted OR Prototheca OR Psyllium OR Pterocarpan* OR Pythium OR Quercetin OR Rheum OR Rhizome OR Rotenone OR Rutin OR Safflower-Oil OR Saponin* OR Saprolegnia OR Sargassum) OR (Scenedesmus OR Seaweed OR Secale-Cereal OR Seed* OR

Selaginellaceae OR Senna-Extract OR Sesame-Oil OR Shallot* OR Silage OR Silymarin OR Sodium-Restricted OR Solanum-Tuberosum OR Soybean* OR Spinacia-Oleracea OR Tannin* OR Tea OR Terpenoid* OR Thiophene* OR Triterpenoid* OR Triticum OR Turpentine OR Ulva OR Undaria OR Usnea OR Vegetable-Protein* OR Vegetable* OR Vegetarian-Diet OR Volvox OR Wine OR Xylem OR Zea Mays)

APPENDIX 2 – SD QUERY

SCIENCE DIRECT FULL TEXT QUERY

The SD query has the same overall structure as the SCI/Medline query, but the format is different due to search engine differences. The SD search engine allows for proximity/adjacency searching, so much shorter queries can be written. A PRE/5 B means that term A precedes term B by five words, and A W/5 B means that term A is within five words of term B.

QUERY = (T NOT S) AND C

T.
(((inhibit* PRE/5 "virus entry") OR (inhibit* PRE/5 "viral entry") OR (inhibit* W/15 replicat* W/15 virus) OR (inhibit* W/15 replicat* W/15 viral)) AND (potent PRE/15 "antiviral activity"))

OR

(((induc* PRE/5 "humoral immun*") AND (induc* PRE/5 "humoral response*") AND ((induc* PRE/5 "antibod* response*") OR (induc* PRE/5 "antibod* production") OR (induc* PRE/5 "virus neutraliz*") OR (induc* PRE/5 "viral neutraliz*"))) OR ((induc* PRE/5 "cellular immun*") AND (induc* PRE/5 "cell mediated immun*") AND ((induc* PRE/5 CD4) OR (induc* PRE/5 CD8) OR (induc* PRE/5 "t cell response*") OR (induc* PRE/5 "t cell immune response*"))) OR ((induc* PRE/5 "innate immun*") AND (induc* PRE/5 "innate antiviral") AND ((induc* PRE/5 "antiviral activity") OR (induc* PRE/5 "antiviral response*"))))

S.
(Severe-Acute-Respiratory-Syndrome OR SARS-Virus OR (SARS AND (coronavirus OR infect* OR virus* OR viral OR epidemic* OR epidemiology OR antibodies OR antibody OR vaccine* OR influenza OR pandemic* OR outbreak* OR syndrome)) OR SARS-patient* OR SARS-transmission OR SARS-Cov)

C.
(Acetabularia OR Achlya OR Acupressure OR Acupuncture OR Algae OR Alkaloid* OR Allium OR Angiosperms OR Anthocerotophyta OR Anthocyanins OR {Antiviral Plant*} OR Aphanomyces OR Apigenin OR {Arachis Hypogaea}

OR Ascophyllum OR {Avena Sativa} OR {Bed Rest} OR Benzoflavones OR {Beta Naphthoflavone} OR Biflavonoids OR Brassica OR Bryophyta OR Caffeine OR {Caloric Restrict*} OR {Calorie Restrict*} OR Capsicum OR {Carbohydrate Restricted} OR Cascara OR {Castor Oil} OR Catechin* OR Caulerpa OR Cereal* OR Chalcone* OR Chara OR Characeae OR Chia OR Chicory OR Chimera OR Chive* OR Chlamydomonas OR Chlorella OR Chlorophyll* OR Chondrus OR Citrus OR {Clove Oil} OR {Cod Liver Oil} OR Coffee OR {Complementary Medicine} OR {Corn Oil} OR {Cottonseed Oil} OR Cotyledon OR Coumarin* OR Coumestrol OR {Croton Oil} OR Cryptophyta OR {Cucumis Sativus} OR Curare OR Cyanophora OR {Daucus Carota} OR {Diabetic Diet} OR {Dietary Supplement*} OR Diosmin OR {Chinese Herbal} OR {Edible Plant*} OR Electroacupuncture OR {EnteraL Nutrition} OR Equisetum OR Ethnobotany OR Ethnomedicin* OR Ethnopharmacology OR Euglena) OR (Euglenida OR Fabaceae OR Fagopyrum OR{Fat Restricted} OR Ferns OR{Fish Oil*} OR Flavanone* OR Flavone* OR Flavonoid* OR Flavonolignan* OR Flavonol* OR Flavoxate OR Flax* OR{Flowering Tops} OR Fruit* OR Fucus OR Garlic OR Genistein OR Ginseng OR Gracilaria OR Gymnosperm* OR Helianthus OR Hepatophyta OR Herb* OR Hesperidin OR Homeopathy OR Hops OR Hordeum OR{Iodized Oil} OR Ipecac OR Isoflavone* OR Kaempferol* OR Kelp OR Lagenidium OR Laminaria OR Laurencia OR Leaf OR Leaves OR Lecithin* OR Lettuce OR Lichens OR Lignan* OR Limonoid* OR{Linseed Oil} OR Lolium OR Luteolin OR{Lycopersicon Esculentum} OR Lycopodiaceae OR Macrocystis OR{Medicago Sativa} OR{Medicinal Plant*} OR{Mediterranean Diet} OR Meristem OR{Mustard Plant} OR Mycorrhizae OR Neolignan* OR Nitella OR{Nutrition Therapy} OR{Nutritional Support} OR Nuts OR Ochromonas OR Olive* OR{Omega 3 Fatty Acid*} OR Onions OR Oomycetes OR Opium OR{Oryza Sativa} OR Panicum OR{Parenteral Nutrition} OR Peas OR Pectin* OR Peronospora OR Phloem OR Phytochemical* OR Phytophthora OR Phytoplankton OR Phytotherapy) OR (Plankton OR{Plant Component*} OR{Plant Epidermis} OR{Plant Extract*} OR{Plant Famil*} OR{Plant Leaves} OR{Plant Oils} OR{Plant Preparation*} OR{Plant Root*} OR{Plant Shoot*} OR{Plant Stem*} OR{Plant Tuber*} OR Plocamium OR Podophyllin OR Polyine* OR Polyphenol* OR Porphyra OR Porphyridium OR Proanthocyanidin* OR{Protein Restricted} OR Prototheca OR Psyllium OR Pterocarpan* OR Pythium OR Quercetin OR Rheum OR Rhizome OR Rotenone OR Rutin OR{Safflower Oil} OR Saponin* OR Saprolegnia OR Sargassum OR Scenedesmus OR Seaweed OR{Secale Cereal} OR Seed* OR Selaginellaceae OR{Senna Extract} OR{Sesame Oil} OR Shallot* OR Silage OR Silymarin OR{Sodium Restricted} OR{Solanum Tuberosum} OR Soybean* OR{Spinacia Oleracea} OR Tannin* OR Tea OR Terpenoid* OR Thiophene* OR Triterpenoid* OR Triticum OR

Turpentine OR Ulva OR Undaria OR Usnea OR{Vegetable Protein*} OR Vegetable* OR{Vegetarian Diet} OR Volvox OR Wine OR Xylem OR{Zea Mays})

SCIENCE DIRECT ABSTRACTS QUERY – LESS RESTRICTIVE CONDITIONS

((inhibit* PRE/5 “virus entry”) OR (inhibit* PRE/5 “viral entry”) OR (inhibit* W/15 replicat* W/15 virus) OR (inhibit* W/15 replicat* W/15 viral) OR (potent PRE/15 “antiviral activity”))

OR

(((induc* PRE/5 “humoral immun*”) OR (induc* PRE/5 “humoral response*”) OR ((induc* PRE/5 “antibod* response*”) OR (induc* PRE/5 “antibod* production”) OR (induc* PRE/5 “virus neutraliz*”) OR (induc* PRE/5 “viral neutraliz*”))) OR ((induc* PRE/5 “cellular immun*”) OR (induc* PRE/5 “cell mediated immun*”) OR ((induc* PRE/5 CD4) OR (induc* PRE/5 CD8) OR (induc* PRE/5 “t cell response*”) OR (induc* PRE/5 “t cell immune response*”))) OR ((induc* PRE/5 “innate immun*”) OR (induc* PRE/5 “innate antiviral”) OR ((induc* PRE/5 “antiviral activity”) OR (induc* PRE/5 “antiviral response*”))))

S.
(Severe-Acute-Respiratory-Syndrome OR SARS-Virus OR (SARS AND (coronavirus OR infect* OR virus* OR viral OR epidemic* OR epidemiology OR antibodies OR antibody OR vaccine* OR influenza OR pandemic* OR outbreak* OR syndrome)) OR SARS-patient* OR SARS-transmission OR SARS-Cov)

C.
(Acetabularia OR Achlya OR Acupressure OR Acupuncture OR Algae OR Alkaloid* OR Allium OR Angiosperms OR Anthocerotophyta OR Anthocyanins OR {Antiviral Plant*} OR Aphanomyces OR Apigenin OR {Arachis Hypogaea} OR Ascophyllum OR {Avena Sativa} OR {Bed Rest} OR Benzoflavones OR {Beta Naphthoflavone} OR Biflavonoids OR Brassica OR Bryophyta OR Caffeine OR {Caloric Restrict*} OR {Calorie Restrict*} OR Capsicum OR {Carbohydrate Restricted} OR Cascara OR {Castor Oil} OR Catechin* OR Caulerpa OR Cereal* OR Chalcone* OR Chara OR Characeae OR Chia OR Chicory OR Chimera OR Chive* OR Chlamydomonas OR Chlorella OR Chlorophyll* OR Chondrus OR Citrus OR {Clove Oil} OR {Cod Liver Oil} OR Coffee OR {Complementary Medicine} OR {Corn Oil} OR {Cottonseed Oil} OR Cotyledon OR Coumarin*

OR Coumestrol OR {Croton Oil} OR Cryptophyta OR {Cucumis Sativus} OR Curare OR Cyanophora OR {Daucus Carota} OR {Diabetic Diet} OR {Dietary Supplement*} OR Diosmin OR {Chinese Herbal} OR {Edible Plant*} OR Electroacupuncture OR {EnteraL Nutrition} OR Equisetum OR Ethnobotany OR Ethnomedicin* OR Ethnopharmacology OR Euglena) OR (Euglenida OR Fabaceae OR Fagopyrum OR{Fat Restricted} OR Ferns OR{Fish Oil*} OR Flavanone* OR Flavone* OR Flavonoid* OR Flavonolignan* OR Flavonol* OR Flavoxate OR Flax* OR{Flowering Tops} OR Fruit* OR Fucus OR Garlic OR Genistein OR Ginseng OR Gracilaria OR Gymnosperm* OR Helianthus OR Hepatophyta OR Herb* OR Hesperidin OR Homeopathy OR Hops OR Hordeum OR{Iodized Oil} OR Ipecac OR Isoflavone* OR Kaempferol* OR Kelp OR Lagenidium OR Laminaria OR Laurencia OR Leaf OR Leaves OR Lecithin* OR Lettuce OR Lichens OR Lignan* OR Limonoid* OR{Linseed Oil} OR Lolium OR Luteolin OR{Lycopersicon Esculentum} OR Lycopodiaceae OR Macrocystis OR{Medicago Sativa} OR{Medicinal Plant*} OR{Mediterranean Diet} OR Meristem OR{Mustard Plant} OR Mycorrhizae OR Neolignan* OR Nitella OR{Nutrition Therapy} OR{Nutritional Support} OR Nuts OR Ochromonas OR Olive* OR{Omega 3 Fatty Acid*} OR Onions OR Oomycetes OR Opium OR{Oryza Sativa} OR Panicum OR{Parenteral Nutrition} OR Peas OR Pectin* OR Peronospora OR Phloem OR Phytochemical* OR Phytophthora OR Phytoplankton OR Phytotherapy) OR (Plankton OR{Plant Component*} OR{Plant Epidermis} OR{Plant Extract*} OR{Plant Famil*} OR{Plant Leaves} OR{Plant Oils} OR{Plant Preparation*} OR{Plant Root*} OR{Plant Shoot*} OR{Plant Stem*} OR{Plant Tuber*} OR Plocamium OR Podophyllin OR Polyine* OR Polyphenol* OR Porphyra OR Porphyridium OR Proanthocyanidin* OR{Protein Restricted} OR Prototheca OR Psyllium OR Pterocarpan* OR Pythium OR Quercetin OR Rheum OR Rhizome OR Rotenone OR Rutin OR{Safflower Oil} OR Saponin* OR Saprolegnia OR Sargassum OR Scenedesmus OR Seaweed OR{Secale Cereal} OR Seed* OR Selaginellaceae OR{Senna Extract} OR{Sesame Oil} OR Shallot* OR Silage OR Silymarin OR{Sodium Restricted} OR{Solanum Tuberosum} OR Soybean* OR{Spinacia Oleracea} OR Tannin* OR Tea OR Terpenoid* OR Thiophene* OR Triterpenoid* OR Triticum OR Turpentine OR Ulva OR Undaria OR Usnea OR{Vegetable Protein*} OR Vegetable* OR{Vegetarian Diet} OR Volvox OR Wine OR Xylem OR{Zea Mays})